April 29, 2005

Elizabeth Hunt
Technical Contact
Hunt Management Services
941 Rhonda Place SE
Leesburg, VA 20175

Dear Ms. Hunt:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for Sulfuric acid, diethyl ester posted on the ChemRTK HPV Challenge Program Web site on February 26, 2004. I commend Dow Chemical Company for its commitment to the HPV Challenge Program.

EPA reviews test plans and robust summaries to determine whether the reported data and test plans will provide the data necessary to adequately characterize each SIDS endpoint. On its Challenge Web site, EPA has provided guidance for determining the adequacy of data and preparing test plans used to prioritize chemicals for further work.

EPA will post this letter and the enclosed comments on the HPV Challenge Web site within the next few days. As noted in the comments, we ask that Dow advise the Agency, within 60 days of this posting on the Web site, of any modifications to its submission. Please send any electronic revisions or comments to the following e-mail addresses: oppt.ncic@epa.gov and chem.rtk@epa.gov.

If you have any questions about this response, please contact Mark Townsend, Acting Chief of the HPV Chemicals Branch, at 202-564-8617. Submit questions about the HPV Challenge Program through the "Contact Us" link on the HPV Challenge Program Web site pages or through the TSCA Assistance Information Service (TSCA Hotline) at (202) 554-1404. The TSCA Hotline can also be reached by e-mail at tsca-hotline@epa.gov.

I thank you for your submission and look forward to your continued participation in the HPV Challenge Program.

Sincerely,

/s/

Oscar Hernandez, Director
Risk Assessment Division

Enclosure

cc: M. E. Weber
J. Willis

EPA Comments on Chemical RTK HPV Challenge Submission:
Diethyl Sulfate

Summary of EPA Comments

The sponsor, the Dow Chemical Company, submitted a test plan and robust summaries to EPA for Sulfuric acid, diethyl ester (Diethyl sulfate, CAS No. 64-67-5) dated January 6, 2004. EPA posted the submission on the ChemRTK HPV Challenge Web site on February 26, 2004.

EPA has reviewed this submission and has reached the following conclusions:

1. Physicochemical Properties and Environmental Fate. The data provided by the submitter for physicochemical endpoints are adequate for the purposes of the HPV Challenge Program. The data provided by the submitter for photodegradation, biodegradation, and fugacity and the proposal to test for stability in water are adequate for the purposes of the HPV Challenge Program.

2. Health Effects. The data submitted for the acute and genetic toxicity endpoints are adequate for the purposes of the HPV Challenge Program. The submitter needs to address deficiencies in the robust summaries. The repeated-dose, reproduction and developmental toxicity endpoints have not been satisfied for the purposes of the HPV Challenge Program. The submitter has not adequately supported the claim that exposure controls justify a reduced testing approach.

3. Ecological Effects. EPA agrees with the submitter's proposal to determine ecological testing needs from the results of a proposed stability in water study.

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.

EPA Comments on the Diethyl Sulfate Challenge Submission

Test Plan

Physicochemical Properties (melting point, boiling point, vapor pressure, partition coefficient and water solubility)

The data provided by the submitter for these endpoints are adequate for the purposes of the HPV Challenge Program.

Environmental Fate (photodegradation, stability in water, biodegradation, fugacity)

The data provided by the submitter for photodegradation, biodegradation and fugacity are adequate for the purposes of the HPV Challenge Program. EPA agrees with the submitter's approach to stability in water testing.

Biodegradation. EPA located an aerobic MITI test that is equivalent to OECD TG 301 (Chemicals Inspection and Testing Institute. 1992. Biodegradation and bioaccumulation data of existing chemicals based on the CSCL Japan, Japan Chemical Industry Ecology-Toxicology and Information Center. ISBN 4-89074-101-1, page 2-101). The submitter could usefully add this information to the biodegradation robust summary.

Health Effects (acute toxicity, repeated-dose toxicity, genetic toxicity, and reproduction/developmental toxicity)

The submitter suggests that exposure to diethyl sulfate is controlled at the site of manufacture and that "no significant exposure to consumers is anticipated to occur." The Guidance for Testing Closed System Intermediates (CSI) for the HPV Challenge Program (http://www.epa.gov/chemrtk/guidocs.htm) allows for a reduced testing protocol provided certain criteria are met. The submitter needs to document that the exposure controls are at least equivalent to CSI criteria in order for reduced testing to be acceptable for the purposes of the HPV Challenge Program.

Adequate data are available for acute and genetic toxicity for the purposes of the HPV Challenge Program. The submitter needs to address deficiencies in the robust summaries.

Repeated-dose toxicity. The data from carcinogenicity studies submitted for this endpoint are not adequate because the robust summary failed to address several important adequacy criteria. These include identification of a NOAEL and a LOAEL, presentation of hematological and clinical chemistry findings, listing of organs examined at necropsy, and other findings. If the claim for reduced testing is not supported, the combined repeated-dose/reproduction/developmental toxicity screening test (OECD TG 422) will satisfy this endpoint.

Reproductive toxicity. If the claim for reduced testing is not supported, the submitter needs to provide data for this endpoint. The combined repeated-dose/reproduction/developmental toxicity screening test (OECD TG 422) will satisfy this endpoint for the purposes of the HPV Challenge Program.

Developmental toxicity. The submitter needs to provide data for this endpoint. If the claim for reduced testing is not supported, the combined repeated-dose/reproduction/developmental toxicity screening test (OECD TG 422) will satisfy this endpoint for the purposes of the HPV Challenge Program. If the claim for reduced testing is supported, the submitter still needs to provide data for this endpoint. In that case, the combined reproductive/developmental screening test (OECD TG 421) will satisfy this endpoint.

Ecological Effects (fish, invertebrates, and algae)

EPA agrees with the submitter's proposed use of the results from the proposed stability in water study to determine the need for aquatic toxicity testing and thus reserves judgment on the need for such testing.

Specific Comments on the Robust Summaries

Health Effects

Acute toxicity. The robust summary for acute oral toxicity in rats is missing the following information: a description of the method used, the range and number of doses, sex and verification of strain and a description of clinical observations. The robust summary for acute inhalation toxicity is missing the following information: a description of the method; sex and strain of rats; and a description of clinical observations. The robust summary for acute dermal toxicity is missing the following information: a description of the method; sex, strain and number of animals used; and a description of clinical observations.

Acute toxicity. The robust summary for acute oral toxicity in rats is missing the following information: a description of the method used, the range and number of doses, sex and verification of strain and a description of clinical observations. The robust summary for acute inhalation toxicity is missing the following information: a description of the method; sex and strain of rats; and a description of clinical observations. The robust summary for acute dermal toxicity is missing the following information: a description of the method; sex, strain and number of animals used; and a description of clinical observations.

Genetic toxicity (in vitro). The robust summary for the HGPRT assay needs to include the identity and concentration of the positive control used. The cell culture conditions of the CHO cells should also be described.

Genetic toxicity (in vivo). The robust summaries of the two micronucleus assays need to identify the positive and negative controls. The number of males and females used should also be identified.

Followup Activity

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.